REMARKS

The Specification has been amended to reflect the correct priority information.

Claim 1 has been canceled. New claims 2-27 have been added. Accordingly, Claims 2-27 are pending in the application.

Applicants submit a preliminary amendment in view of a reference cited in Applicants' Information Disclosure Statement submitted with the filing of the parent application on February 25, 2000. The reference, WO 99/07389, is based on U.S. Application No. 08/907,598 (now U.S. Patent No. 6,139,833), filed August 8, 1997, to Burgess, *et al.*, herein "Burgess". The reference discloses a vector, VICTR 12, in Figure 2. This vector contains a PGK promoter operably linked to a puromycin gene (a selectable marker) which is operably linked to a splice donor sequence. These components are integrated into both of the vector long terminal repeat regions.

This reference was cited by the Examiner in Applicants' co-pending Application No. 09/455,659 (U.S. Patent No. 6,602,686). In that case, claims directed to eukaryotic cells *in vitro* were amended to recite that the endogenous gene was translated. Claims directed to methods for gene activation were also amended to recite that the endogenous gene is translated. Accordingly, in the present case, Applicants have amended claims directed to cells and methods to contain that recitation.

Claim 2 is based on claims 20 and 89 in the parent case and claim 89 in co-pending Application No. 09/455,659. Claim 3 is based on claims 66 and 90 in the parent case and claim 90 in U.S. Application No. 09/455,659. Claims 4-11 are based on claims 21-28 in the parent case. Claims 12-16 are based on claims 10 and 61-65 in the parent case. Claims 17-20 are based on claims 67-70 in the parent case. Claim 21 is based on claim 72 in the parent case. Claim 22 is based on claims 73 and 89 in the parent case. Claim 23 is based on claims 74-77 in the parent case. Claim 24 is based on claim 89 in the parent case and claim 87 in Application No. 09/455,659. Claim 25 is based on claim 90 in the parent case and claim 88 in Application No. 09/455,659.

Applicants submit that the amendments are effective over Burgess for the same reasons accepted by the Examiner in the co-pending parent case. These reasons are discussed below.

Burgess Does Not Disclose or SuggestProtein Expression From An Endogenous Gene

Burgess produces a fusion transcript by splicing the vector splice donor onto the endogenous splice acceptor. Gene expression from the Burgess vectors was limited to the nucleic acid level. Since Burgess was limited to expression of endogenous nucleic acid, there would have been no motivation to express a fusion protein from the selectable marker exon in the Burgess vector. Burgess actually teaches away from translation of the endogenous gene, as is discussed in detail immediately below.

Burgess Teaches Away From Protein Expression From An Endogenous Gene

The Burgess vectors at issue contain a selectable marker 3′ to a promoter and linked to a 3′ splice donor. The selectable marker lacks a poly A site. The poly A site is supplied by the trapped gene. When a gene is trapped, therefore, a fusion transcript is produced containing the selectable marker RNA and RNA from the trapped gene. The selectable marker RNA is translated, but the RNA from the endogenous gene is not translated. The purpose of producing RNA from the endogenous gene is to provide nucleic acid sequence information about the gene.

The goal of Burgess is to provide a "knock-out" mouse for genes in the genome that are not easily accessible and/or have DNA binding function (column 6:1-9, column 8:19-32). Towards this goal, the identity of the "knocked-out" gene is determined. Thus, the Burgess vectors provide two functions: "knock-out" and identification of a gene. Accordingly, the vectors contain sequences that disrupt expression of a gene and sequences that produce a fusion transcript between the marker and the endogenous gene. The disrupted gene is identified by endogenous gene sequences on the fusion transcript. Accordingly, identification is by nucleic acid

sequencing only. For uses of the fusion transcript, see Burgess, column 7, line 55 through column 8, lines 1-9; Figure 4 and figure legend on column 5:4-7; column 5:48-51; column 17:14-27; column 24:35-50; columns 35-37 (sections 5.5 through 5.6); column 37 (section 5.7).

Thus, Burgess does not disclose or suggest the production of a protein from the endogenous gene.

On the contrary, Burgess specifically teaches away from producing protein from the endogenous gene.

> "All of the traps of the VICTR series are designed such that a fusion transcript is formed with the trapped gene. For all but VICTR 1, the fusion contains cellular exons that are located 3′ to the gene trap insertion. All of the flanking exons may be sequenced according to the methods described in the following section. To facilitate sequencing, specific sequences are engineered onto the ends of the selectable marker (e.g., puromycin coding region). Examples of such sequences include, but are not limited to unique sequences for priming PCR, and sequences complementary to the standard M13 forward sequencing primer. **Additionally, stop codons are added in all three reading frames to ensure that no anomalous fusion proteins are produced.** All of the unique 3′ sequences are followed immediately by the synthetic 9 base pair splice donor sequence. This keeps the size of the exon comprising the selectable marker (puro gene) at a minimum to best ensure proper splicing, and positions the amplification and sequencing primers immediately adjacent to the flanking "trapped" exons to be sequenced as part of the construction of a library database."

Emphasis added. See Burgess, column 22, lines 45-64.

This shows that Burgess obtains expression of the endogenous gene only to obtain nucleic acid sequence information. Protein expression is neither disclosed nor suggested. In fact, Burgess teaches *preventing protein expression* from the endogenous gene to avoid problems with marker expression that could result from the production of anomalous fusion proteins produced by fusion of a marker protein with protein from the endogenous gene. Moreover, to express the endogenous protein would defeat the

purpose, which was to knock-out endogenous protein expression. Accordingly, Burgess teaches away from the production of endogenous protein sequences.

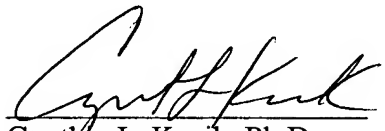
Accordingly, no new matter has been added with these claims.

CONCLUSION

On the basis of the foregoing amendments and remarks, Applicants respectfully submit that the pending claims are in condition for allowance. If the Examiner believes that a telephone conversation is in order, he is invited to contact Applicants' attorney, Anne Brown, at 216-426-3586 or Cynthia L. Kanik, Ph.D., at 617-227-7400.

Respectfully submitted,

LAHIVE & COCKFIELD, LLP



Cynthia L. Kanik, Ph.D.
Reg. No. 37, 320
Attorney for Applicants

28 State Street
Boston, MA 02109
Tel. (617) 227-7400

Dated: **February 2, 2004**